II. REMARKS

Upon entry of the present amendment, claims 1 to 29 will be pending. A marked up version showing the amendments to the specification and the claim is attached hereto as Exhibit A.

A. Regarding the Amendments

The specification has been amended to preserve the proprietary nature of the trademarked term "Sepharose" by using the term as an adjective to refer to a "gel" matrix. As such, the amendment merely addresses a formality and does not add new matter.

Claim 1 has been amended to insert the term "functional" with respect to the peptide portions of promyostatin. The amendment is supported, for example, at page 21, lines 12-16, and, therefore, does not add new matter.

B. Regarding the Species Election

It is stated in the Office Action that a search of the various sequences disclosed in the subject application would constitute an undue search burden given the ever-increasing size of the databases and, therefore, the species election has been made final. As discussed below, the issue as to whether a search would constitute an undue burden is not the standard for requiring a species election. Nevertheless, Applicants maintain that a requirement of separate searches for each of the sequences in separate patent applications would constitute a far greater burden on U.S. Patent Office resources, including clerical and examination resources, than would a search by the Examiner of all of the sequences in the subject application. As was previously pointed out, the substantial sequence homology would necessarily result in a search of art relevant to any one of the sequences being relevant to each and every one of the other sequences. As such, the requirement that each of the polynucleotides encoding the various promyostatin (GDF-8) polypeptides be examined in separate applications cannot be justified given the substantial sequence homology shared among the sequences and the substantial duplication of effort that would be required for the U.S. Patent Office to search each sequence in separate applications.

Notwithstanding the above reason for removing the species election requirement, Applicants point out that the standard for determining whether various species should be examined together is not whether the search would be a burden but, instead, is whether the species share a "commonality of operation, function and effect" (MPEP § 806.04(e)). As disclosed in the specification, the promyostatin polypeptides encoded by the claimed polynucleotides share a commonality of operation, function and effect and, therefore, properly should be examined together. Similarly, each of the encoded "peptide portions" of promyostatin share a commonality of operation, function and effect, including, for example, the mature C-terminal portion, which has myostatin activity, and the prodomain, which can inhibit the ability of myostatin to activate signal transduction (see, for example, Example 7, pages 105-106). Accordingly, Applicants respectfully request that the Examiner withdraw the species election requirement and examine the sequences together.

Applicants also point out that, as set forth in the handout provided at the November 15, 2001, PTO Customer Partnership meeting for Bio/Chemical Practitioners, in the section entitled "Restriction Practice", "allowable linking claims(s) requires withdrawal of restriction as to any claim(s) depending from or otherwise including all of the limitations of the allowable linking claim" (see Exhibit B, copy of above-mentioned section entitled "Restriction Practice"; page 1, third panel). Applicants point out that claim 1 of the subject application is a genus claim linking species claims. As indicated in Exhibit B (page 2, third panel), if claim 1 is determined allowable, all of the inventions become subject to examination (i.e., all of the polynucleotide encoding the disclosed GDF-8 polypeptides of the subject application). For the reasons set forth below, it is submitted that claim 1 is allowable and, therefore, it is respectfully requested that the Examiner rejoin and examine each of the polynucleotide species as set forth in the claims.

C. Regarding the Specification

The specification is objected to for using the term "Sepharose" without preserving the proprietary nature of the trademark. The specification has been amended to address this informality. As such, it is respectfully requested that the objection be withdrawn.

D. Double Patenting Rejection

The rejection of claims 1 to 4, 9 to 22 and 27 to 29 under the judicially established doctrine of obviousness-type double patenting over claims 2 to 11 of U.S. Pat. No. 5,827,733 is respectfully traversed.

Applicants recognize the overlapping subject matter, and have filed the subject application to prosecute the broader generic claims. As such, Applicants respectfully defer responding to this ground of rejection until a notice is received that the claims in the subject application are otherwise in condition for allowance.

The provisional rejection of claims 1 to 4, 9 to 22 and 27 to 29 under the judicially established doctrine of obviousness-type double patenting over claims 21 to 23 of copending application U.S. Serial No: 09/628,112 is respectfully traversed.

Although the rejection is traversed, Applicants respectfully defer responding to the rejection until a notice is received that the claims in the subject application and/or U.S. Serial No. 09/628,112 are otherwise in condition for allowance.

E. Rejections under 35 U.S.C. § 112

The objection to the specification and corresponding rejection of claims 1 to 4, 9 to 22 and 27 to 29 under 35 U.S.C. § 112, first paragraph, as allegedly lacking an adequate written description are respectfully traversed.

It is stated in the Office Action that the specification discloses that the C-terminal region of myostatin can interact with its receptor and affect signal transduction, and that the prodomain of promyostatin can interact with the mature or parent protein. It is alleged, however, that the disclosure of these two regions is not sufficient to define the claimed genus, which encompasses subgenera of molecules having diverse functions and, therefore, diverse functional requirements (paragraph bridging pages 4-5). It is stated, for example, that no structural characteristics or sequences required

for any particular function have been set forth, and that there is no description of features that would be required for activators, inhibitors or other molecules.

Applicants point out, however, that the specification discloses three regions of a promyostatin polypeptide, including a signal peptide (about amino acid residues 1 to 20), a prodomain (about amino acid residues 20 to 262), and a mature C-terminal domain (myostatin; about amino acid residues 267 to 375), and further discloses such regions in promyostatin polypeptides expressed in various vertebrate species, including, for example, murine and bovine species and humans (see page 22, line 8 to page 23, line 10; and page 32, lines 20-29). As such, the specification discloses the regions of promyostatin associated with specific functions (see, for example, page 21, lines 6-27). The specification also discloses that a peptide comprising the C-terminal portion of promyostatin specifically binds to the activin receptor (Example 7, page 105, lines 3-26), and further provides an assay for detecting such specific binding, which one skilled in the art would recognize as useful for identifying additional peptide portions of promyostatin having such an activity (see, also, Example 9, pages 107-109). In view of this disclosure, the skilled artisan would have known that Applicants were in possession of peptide portions of promyostatin that can activate myostatin signal transduction.

The specification also discloses that a peptide comprising the prodomain of promyostatin inhibits myostatin binding to activin receptor (Example 7, page 105, line 27, to page 106, line 2) and, therefore, is an inhibitor of myostatin signal transduction. In addition, the skilled artisan would have known that the assay as disclosed in Example 7 can be used to identify other peptide portions of promyostatin that inhibit myostatin signal transduction. The specification further discloses mutant promyostatin polypeptides that are not susceptible to proteolytic cleavage, or example, promyostatin polypeptides having a mutation in the proteolytic cleavage site, resulting in a polypeptide that cannot be cleaved to generate an active myostatin polypeptide and that can have dominant negative activity (see page 33, line 26, to page 34, line 5). As such, it is submitted that one skilled in the art would have known that Applicants were in possession of promyostatin polypeptides and peptide portions thereof that can inhibit myostatin signal transduction.

The specification also discloses additional molecules involved a myostatin signal transduction pathway, including, for example, the Smad proteins, and further discloses that the phosphorylation state of the Smad proteins is dependent on myostatin signal transduction (see page 44, lines 8-21). As such, the skilled artisan would have known that, in addition to the activin receptor binding assay described in Example 7, an assay based on a determination of Smad phosphorylation state can be used to identify a peptide portion of a promyostatin polypeptide that can affect myostatin signal transduction.

In summary, the specification discloses peptide portions of promyostatin that can activate or that can inhibit myostatin signal transduction, exemplifies such peptides in promyostatin polypeptides from various vertebrate species, and provides assays that, as disclosed in the specification, can identify peptide portions of a promyostatin polypeptide that can affect myostatin signal transduction. As such, it is submitted that specification adequately describes the claimed subject matter such that one skilled in the art would have known that the Applicants were in possession of the invention. Accordingly, it is respectfully requested that the objection to the specification be withdrawn and that the corresponding rejection of claims 1 to 4, 9 to 22 and 27 to 29 as allegedly lacking an adequate written description be removed.

The objection to the specification and corresponding rejection of claims 1 to 4, 9 to 22 and 27 to 29 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement are respectfully traversed.

It is acknowledged in the Office Action that the specification enables polynucleotides encoding mature myostatin proteins and the promyostatin proregion. It is alleged, however, that the specification does not enable polynucleotides encoding all functional peptide portions. It is stated, for example, that the claims "encompass polynucleotides encoding all "peptide portions", which are defined by Applicant as having many different functions, as well as oligonucleotides." (Office Action, paragraph bridging pages 6-7). Applicants point out, however, that, while a peptide portion of promyostatin can act in various ways, the "function" of the claimed peptides is specifically defined

as "having or affecting an activity associated with the stimulation or inhibition ... myostatin signal transduction activity..." (page 21, lines 6-12). Thus, while a peptide of the invention can act in various ways to cause diverse effects, the function is clearly defined. In this respect, the specification provides specific examples of such peptides that can activate or inhibit myostatin signal transduction, and further provides routine assays for determining that a peptide portion of promyostatin can have or affect an activity associated with the stimulation or inhibition of myostatin signal transduction.

It is also stated in the Office Action that, while recombinant techniques are available, it is not routine in the art to screen large numbers of polynucleotides where the expectation of obtaining the desired activity is unpredictable (Office Action, sentence bridging pages 6-7). Applicants are unaware of the basis for correlating an expectation of obtaining a peptide having a desired activity with whether a screening assay is deemed to be routine. Indeed, methods of screening randomly generated molecules to identify those that bind a particular receptor or have a desired activity are well known and routine in the art.

It is well recognized that undue experimentation is not necessarily correlated to how much work may be necessary, and that "a considerable amount of experimentation is permissible if it is merely routine...." (see In re Wands 8 USPQ2d, 1400 (Fed. Cir. 1988, at 1404; citing In re Jackson 217 USPQ 804 (Bd. App. 1982), at 807). In the present case, the exemplified activin receptor screening assay (Example 7) can be performed as a matter of routine. As such, in view of Applicants' disclosure that specific portions of promyostatin are associated with the ability to activate or inhibit myostatin signal transduction, it is submitted that no more than routine experimentation using methods and peptide portions of promyostatin as disclosed in the specification would have been required for the skilled artisan to make various and numerous peptide portions of promyostatin and examine such peptides for the ability to affect myostatin signal transduction.

As such, in view of the exemplified functional peptide portions of promyostatin and the methods for determining whether a peptide activates or inhibits myostatin signal transduction, it is submitted that undue experimentation would not have been required for one skilled in the art to make and use the claimed polynucleotides. Accordingly, it is respectfully requested that the objection to

the specification be withdrawn and corresponding rejection of claims 1 to 4, 9 to 22 and 27 to 29 as allegedly lacking enablement be removed.

The rejection of claims 1 to 4, 9 to 22 and 27 to 29 under 35 U.S.C. § 112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter of the invention is respectfully traversed.

It is alleged in the Office Action that the terms "peptide portions", "functional peptide portions" and "proteolytic fragments" are indefinite because the specification does not define the limits of such portions or fragments and because there is no definition of "functional." As such, it is alleged that one skilled in the art would not know what molecules meet the limitations of the claims.

Applicants point out that the terms "peptide portion" and "proteolytic fragment" are defined at page 18, lines 4-28, and, as was pointed out with respect to the "written description" rejection, the term "functional peptide portion", when used with respect to a promyostatin polypeptide, is defined at page 21 (see lines 6-16) of the specification, wherein it is "characterized, in part, by having or affecting an activity associated with the stimulation or inhibition of GDF signal transduction" and, more specifically, myostatin signal transduction (see, also, page 43, 16-28). Thus, the specification clearly defines the terms as used in the claims, and further provides examples of methods for determining whether a peptide portion of a promyostatin polypeptide has a function related to myostatin signal transduction (see Examples 7 and 9, demonstrating, for example, myostatin binding to the activin receptor and inhibition of such binding by the promyostatin prodomain peptide).

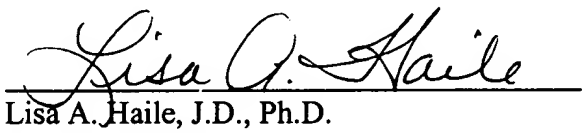
As such, it is submitted that the skilled artisan, reading the claims in view of the specification, would know the subject matter encompassed within the claims. Accordingly, it is respectfully requested that the rejection of the claims under 35 U.S.C. § 112, second paragraph, be removed.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, the Commissioner is authorized to charge any fee (or credit any overpayment) to Deposit Acct. No. 50-1355.

The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Respectfully submitted,

Dated: January 29, 2002



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Encls. Exhibits A and B

EXHIBIT A

MARKED UP VERSION SHOWING THE AMENDMENTS TO THE SPECIFICATION AND THE CLAIM

A. In the Specification

The paragraph bridging pages 88-89 was amended by adding the term "gel", as shown by the underlining (Note: the underlining of the reference in the following paragraph was in the application as filed, and is not an indication that the reference was added by the present amendment)

Monoclonal antibodies can be isolated and purified from hybridoma cultures by a variety of well established techniques, including, for example, affinity chromatography with Protein-A SEPHAROSE gel, size exclusion chromatography, and ion exchange chromatography (Coligan et al., *supra*, 1992, see sections 2.7.1-2.7.12 and sections 2.9.1-2.9.3; see, also, Barnes et al., "Purification of Immunoglobulin G (IgG)," in Meth. Molec. Biol. 10:79-104 (Humana Press 1992), which is incorporated herein by reference). Methods of *in vitro* and *in vivo* multiplication of monoclonal antibodies is well known to those skilled in the art. Multiplication *in vitro* can be carried out in suitable culture media such as Dulbecco's Modified Eagle Medium or RPMI 1640 medium, optionally replenished by a mammalian serum such as fetal calf serum or trace elements and growth sustaining supplements such as normal mouse peritoneal exudate cells, spleen cells, bone marrow macrophages. Production *in vitro* provides relatively pure antibody preparations and allows scale-up to yield large amounts of the desired antibodies. Large scale hybridoma cultivation can be carried out by homogenous suspension culture in an airlift reactor, in a continuous stirrer reactor, or in immobilized or entrapped cell culture. Multiplication *in vivo* can be carried out by injecting cell clones into mammals histocompatible with the parent cells, for example, syngeneic mice, to cause growth of antibody producing tumors. Optionally, the animals are primed with a hydrocarbon, especially oils such as pristane (tetramethylpentadecane) prior to injection. After one to three weeks, the desired monoclonal antibody is recovered from the body fluid of the animal.

The paragraph at page 103, lines 6-16, was amended as follows:

In order to elucidate the biological activity of myostatin, large quantities of myostatin protein were purified for bioassays. Stable Chinese hamster ovary (CHO) cell lines producing high levels of myostatin protein were generated by co-amplifying a myostatin expression cassette with a dihydrofolate reductase cassette using a methotrexate selection scheme (McPherron et al., *supra*, 1997). Myostatin was purified from the conditioned medium of the highest producing line by successive fractionation on hydroxyapatite, lentil lectin SEPHAROSE gel, DEAE agarose, and heparin SEPHAROSE gel. Silver stain analysis revealed that the purified protein obtained following these four column chromatography steps (referred to as "heparin eluate") consisted of two species with molecular masses of approximately 35 kilodaltons (kDa) and 12 kDa.

B. In the Claims

Claim 1 was amended as follows:

1. (Amended) An isolated polynucleotide encoding a promyostatin polypeptide or a functional peptide portion thereof, or a polynucleotide complementary thereto.